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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,273	01/18/2001	Michael Bittner	IVGN 616	1332

23358 7590 09/22/2008
INVITROGEN CORPORATION
C/O INTELLEVATE
P.O. BOX 52050
MINNEAPOLIS, MN 55402

EXAMINER	
CROW, ROBERT THOMAS	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/766,273	BITTNER ET AL.
	Examiner	**Art Unit**
	Robert T. Crow	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-43 and 45-79* is/are pending in the application.

4a) Of the above claim(s) *39-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 July 2008 has been entered.

Status of the Claims

2. This action is in response to papers filed 10 July 2008 in which no claims were amended, claims 1-29, 31-32, 34, 36, 38, and 44 were canceled, and new claims 45-79 were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant’s arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 39-43 were previously withdrawn.

Claims 45-79 are under prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 45-49, 58-59, 61-63, 67-72, and 74-79 rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and further in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997).

Regarding claims 45, 67, and 70-71, Mirkin et al teach a method for assaying a first sample for a first probe. In a single exemplary embodiment, Mirkin et al teach providing a substrate attached to a first target; namely, a substrate comprising a plurality of initial type of oligonucleotides attached to the substrate in an array of spots, wherein each spot contains a different type of oligonucleotide (page 40, line 30-page 41, line 11). The plurality of different initial type of oligonucleotides attached in an array of spots is the claimed plurality of different targets attached to a substrate. Because there are different types of targets, each target can preferentially bind to a

corresponding different probe polynucleotide. The substrate is contacted with the first sample, wherein the first sample is suspected of comprising the first probe; namely, analyte DNA is added to the substrate (Figure 13B); the instantly claimed “first probe” is the analyte DNA of Figure 13B, and the instantly claimed "targets” are the adsorbed thiol modified DNA of Figure 13B. The first probe comprises a first probe polynucleotide comprising a first tag sequence which does not bind to the first target and a first binding sequence which does bind to the first target, and wherein contacting the substrate with the first sample takes place under conditions in which the first binding sequence can bind to the first target; namely, Figure 13B shows part of the first probe hybridizing to the immobilized targets through a first binding sequence, and the remainder of the first probe is a first tag sequence available to bind to DNA modified nanoparticles. The DNA modified nanoparticles of Figure 13B are the tag-binding conjugate, which binds to the first tag sequence. The nanoparticles are a semiconductor nanoparticles (page 19, lines 24-34), and determining if the semiconductor nanocrystal is associated with the substrate occurs because Mirkin et al teach color changes resulting from binding on the substrate are noted (page 83, lines 18-20 and Figure 13B, last step).

It is noted that claim 67 requires applying a light source that **can** excite the semiconductor nanocrystal. The use of the word “can” does not necessarily require an active method step specifically requiring the light source to excite, and thereby induce emission from, the semiconductor nanocrystal; rather, the phrase “can be" merely requires the light source is capable of exciting, and thereby inducing emission from, the semiconductor nanocrystal.

While Mirkin et al teach the use of semiconductor nanocrystals comprising CdS (i.e., claim 71; page 19, lines 30-35), Mirkin et al do not teach each conjugate comprises different semiconductor nanocrystals with different fluorescence characteristics (i.e., claims 45 and 67) or that the nanocrystals comprise shells (i.e., claims 70-71).

However, Weiss et al teach the use of semiconductor nanocrystals attached to probes (i.e., affinity molecules) to determine the presence of a detectable substance in a material (Abstract), wherein the probes (i.e., affinity molecules) are nucleic acids (column 6, lines 50-67) and wherein a plurality of differently colored semiconductor probes each having different semiconductor nanocrystals are used by shining light on the crystal and detecting the fluorescence (i.e., claims 45 and 67; column 1, lines 50-65). The nanocrystals encompass shell particles of CdS (i.e., claims 70-71; column 6, lines 17-35). Weiss et al also teach the particles have the added benefit of allowing detection of a plurality of detectable substances without overlap of the signals (column 6, lines 35-47). Thus, Weiss et al teach the known technique of using different semiconductor nanocrystals in each probe (i.e., claim 45), wherein the nanocrystals are excited and fluoresce (i.e., claim 67), and have CdS shells (i.e., claims 70-71).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of different probes having semiconductor nanocrystals as taught by Mirkin et al so that each probe has a different semiconductor nanocrystal as taught by Weiss et al to arrive at the instantly claimed method with a reasonable expectation of success. The modification would result in a method wherein each probe has a different semiconductor

nanocrystal (i.e., claim 45), wherein the nanocrystals are excited and fluoresce (i.e., claim 67), and have CdS shells (i.e., claims 70-71). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing simultaneous detection of a plurality of detectable substances without overlap as explicitly taught by Weiss et al (column 6, lines 35-47). In addition, it would have been obvious to the ordinary artisan that the known technique of using the different nanocrystals as taught by Weiss et al could have been applied to the method of Mirkin et al in with predictable results because the known technique of using the different nanocrystals as taught by Weiss et al predictably result in detection of binding events during a microarray hybridization assay.

While Mirkin et al also teach a plurality of different targets attached to the substrate and each of the different targets preferentially binds a different probe polynucleotide (e.g., a plurality of oligonucleotides are provided in an array to detect multiple different nucleic acids; page 40, line 32-page 41, line 11), neither Mirkin et al nor Weiss et al teach each different first probe can be separately determined by determining if each different semiconductor nanocrystal is associated with the substrate (i.e., separate determination of each binding event; claim 45).

It is noted, however, that claim 45 requires that each different first probe **can be** separately determined by determining if each different semiconductor nanocrystal is associated with the substrate. The use of the phrase “can be” does not necessarily require an active method step requiring the separate determination of each different semiconductor nanocrystal; rather, the phrase “can be" merely requires that each

different semiconductor nanocrystal is capable of being separately detected. Because Weiss et al teach the different semiconductor nanoparticles allow detection without overlap of the signals (column 6, lines 35-47), modification of the method of Mirkin et al with the teachings of Weiss et al results in each different probe having a corresponding different semiconductor nanocrystal that is capable of being separately detected.

Furthermore, while not actually required by claim 45, the separate determination of whether or not each different semiconductor nanocrystal is associated with the substrate would also be obvious in view of Pinkel et al, who teach a method of assaying samples for probes by using a biosensor array to detect nucleic acid binding complexes (Abstract), wherein each binding event is separately determined; namely, simultaneous assaying of binding components of a test sample are done on by discrete detection at individual locations (i.e., bundles of fibers; Abstract) with the added benefit that the discrete addressing assists in rapid sample identification (Abstract). Thus, Pinkel et al teach the known technique of separately determining each binding event on an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the detection of multiple different binding events as taught by Mirkin et al in view of Weiss et al so that the multiple different binding events are separately determined as taught by Pinkel et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in method having the added advantage of allowing rapid sample identification as explicitly taught by Pinkel et al (Abstract). In

addition, it would have been obvious to the ordinary artisan that the known technique of using the separate determination of each binding event on an array of Pinkel et al could have been applied to the method of Mirkin et al in view of Weiss et al with predictable results because the separate determination of Pinkel et al predictably results in detection of all of the binding events during a microarray hybridization assay.

Regarding claim 46, the method of claim 45 is discussed above. Mirkin et al also teach the substrate is a slide (page 82, lines 30-34).

Regarding claim 47, the method of claim 45 is discussed above. Mirkin et al further teach the substrate comprises a plurality of different targets; namely, the substrate has rows of spots, each spot containing a different type of oligonucleotide (page 41, lines 2-11).

Regarding claim 48, the method of claim 47 is discussed above. Mirkin et al teach the substrate comprises a microarray (page 40, lines 32-35).

Regarding claim 49, the method of claim 45 is discussed above. Mirkin et al also teach the first probe polynucleotide is produced from an amplification process comprising a polymerase chain reaction; namely, the nucleic acid being detected is in a polymerase chain reaction (i.e., PCR) solution (page 24, lines 18-24).

Regarding claims 58 and 59, the method of claim 45 is discussed above. Mirkin et al further teach the first tag sequence is located at or nearer either the 5’ end (i.e., claim 58) or the 3’ end (i.e., claim 59) of the first probe polynucleotide; namely, oligonucleotides are functionalized for attachment to solid surfaces at either their 3’ termini or their 5’ termini (page 21, line 34-page 22, line 22). The end that is attached

dictates which end is the overhang of the linking oligonucleotide (i.e., the first tag sequence) will be on; i.e., if the first target is attached to the slide on its 3' end, the first tag sequence will be on the 3' end of the probe. Because Mirkin et al teach attachment of the first target to the substrate at either end, and because the attachment end of the first target dictates which end the first tag is located on, Mirkin et al teach the location of the tag sequence at either end of the first probe polynucleotide.

Regarding claim 61, the method of claim 45 is discussed above. Mirkin et al teach contacting the sample with the first target takes place prior to contacting the sample with the first tag-binding conjugate (Example 10).

Regarding claim 62, the method of claim 45 is discussed above. With respect to contacting the sample with the first target after contacting the sample with the first tag-binding conjugate, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C. Because Mirkin et al teach all of the steps required in claim 62, the claim is obvious over Mirkin et al in view of Weiss et al and Pinkel et al.

Regarding claim 63, the method of claim 45 is discussed above. Mirkin et al also teach contacting the sample with the first target takes place simultaneously contacting the sample with the first tag-binding conjugate (Example 10). It is noted that during the final step of hybridization step of Example 10 (page 83, lines 10-20), both the sample (i.e., the linking oligonucleotide) and the first tag-binding conjugate (i.e., the complementary oligonucleotide attached to the semiconductor nanoparticle) are both

present; therefore, the contacting of the sample with the first target and the first tag-binding conjugate is occurring simultaneously.

Regarding claims 68 and 69, the method of claim 45 is discussed above. Mirkin et al further teach the first semiconductor nanocrystal comprises a core of CdSe (page 19, lines 24-26).

Regarding claim 72, the method of claim 45 is discussed above. Mirkin et al teach the sample is assayed to determine if the probe is present in the sample; namely, the method detects hybridized nucleic acids (Abstract).

Regarding claim 74, the method of claim 45 is discussed above. Mirkin et al also teach the substrate is washed, by rinsing with buffer, prior to determining of the first semiconductor nanocrystal is associated with the first target (page 83, lines 10-20).

Regarding claim 75, the method of claim 45 is discussed above. Mirkin et al further teach a medium is added to the substrate to dilute the concentration of the first semiconductor nanocrystal prior to determining if the semiconductor nanocrystal is associated with the first target; namely, the substrate is removed and rinsed with a buffer (page 83, lines 10-20). Thus, after removal, the nanoparticles are at a concentration on the substrate, and the rinsing of the substrate, which introduces more fluid (but not more nanoparticles) to the substrate, dilutes the nanoparticles.

Regarding claim 76, the method of claim 45 is discussed above.

It is noted that claim 76 requires that each different first probe bound to the different target **can be** separately determined through a different identified position at which each different target is attached to the substrate. The use of the phrase “can be”

does not necessarily require an active method step requiring the separate determination of each probe polynucleotide at a different identified position; rather, the phrase “can be" merely requires that each different probe polynucleotide is capable of being separately detected. Because Mirkin et al each spot contains a different type of oligonucleotide (page 40, line 30-page 41, line 11) and because Weiss et al teach the different semiconductor nanoparticles each allow detection without overlap of the signals (column 6, lines 35-47), modification of the method of Mirkin et al with the teachings of Weiss et al results in each different probe at a different position having a corresponding different semiconductor nanocrystal that is capable of being separately detected.

Furthermore, while not actually required by claim 76, the separate determination at each different identified position of the substrate would also be obvious in view of Pinkel et al, who teach the binding of each different probe polynucleotide to its corresponding different target can be separately determined through a different identified position at which each different target is attached to the substrate; namely, the substrate comprises fibers to which the nucleic acids (i.e., binding partners) are attached, and each fiber is uniquely identified and discretely addressed to detectors, which has the added advantage of allowing transmission of unique pattern to assist in rapid identification of the sample in the sensor (Abstract). Thus, Pinkel et al teach the known technique of using different identified positions.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Mirkin

et al in view of Weiss et al and Pinkel et al so that the targets are separately determined through the different identified positions of Pinkel et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing transmission of unique pattern to assist in rapid identification of the sample in the sensor as explicitly taught by Pinkel et al (Abstract). In addition, it would have been obvious to the ordinary artisan that the known technique of using the different identified positions of Pinkel et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the different identified positions of Pinkel et al predictably results in high quality data from hybridization assays.

Regarding claim 77, the method of claim 45 is discussed above.

It is noted that claim 77 requires that each different first probe hybridized to each different target **can be** separately determined by the conditions under which it hybridizes. The use of the phrase “can be” does not necessarily require an active method step requiring the separate determination of each probe polynucleotide based on the conditions; rather, the phrase “can be" merely requires that each different probe polynucleotide is capable of being separately detected. Because Mirkin et al each spot contains a different type of oligonucleotide (page 40, line 30-page 41, line 11), which can bind under different conditions because they are different molecules, and because Weiss et al teach the different semiconductor nanoparticles each allow detection without overlap of the signals (column 6, lines 35-47), modification of the method of Mirkin et al

with the teachings of Weiss et al results in each different first probe hybridized to each different target having a corresponding different semiconductor nanocrystal that is capable of being separately detected.

Furthermore, while not actually required by claim 77, the separate determination based on hybridization conditions would also be obvious in view of Pinkel et al, who teach the hybridization of each different probe polynucleotide to its corresponding different target can be separately determined by the conditions under which it hybridizes; namely, hybridization occurs under defined stringency conditions, which has the added advantage of allowing control of the amount mismatch sequences hybridized (column 6, lines 16-30), which prevents false positive from being created in an assay. Thus, Pinkel et al teach the known technique of using separate determination conditions.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Mirkin et al in view of Weiss et al and Pinkel et al so that each different first probe hybridized to each different target is separately determined based on hybridization conditions as taught by Pinkel et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing false positive from being created in an assay as a result of controlling the amount of mismatch hybrids as explicitly taught by Pinkel et al (column 6, lines 16-30). In addition, it would have been obvious to the ordinary artisan that the

known technique of using the separate determination conditions of Pinkel et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the separate determination conditions of Pinkel et al predictably results in high quality data from hybridization assays.

Regarding claim 78, the method of claim 45 is discussed above. Mirkin et al also teach the method wherein each different probe polynucleotide is bound to a different tag-binding conjugate which comprises a different semiconductor nanocrystal; namely, each spot in the array is assayed with oligonucleotide nanoparticle conjugates (page 41, lines 1-11), wherein the nanoparticle is a semiconductor nanoparticle (page 19, lines 24-34), and wherein the oligonucleotide nanoparticle conjugates are attached to the same type of particle (Example 10 and Figure 13B). The broad limitation “a different semiconductor nanocrystal” is interpreted in the instant claim to mean the tag-binding conjugates are each bound to a different (i.e., physically distinct) particle (e.g., Figure 13B).

Regarding claim 79, the method of claim 45 is discussed above. Mirkin et al also teach the target is a polynucleotide is located in a cell, which may be fixed or unfixed (page 24, lines 18-20).

Response to Arguments

Applicant's arguments filed 10 July 2008 (i.e., the “Remarks”) have been fully considered but they are not persuasive for the reason(s) listed below.

A. The examiner would like to thank Applicant for the Table provided on pages 9-10 of the Remarks, which has aided the examiner tremendously in preparation of this Office Action.

B. Applicant argues on pages 8 and 9 of the Remarks that new claim 45 included “determining if a fluorescence emission from the first semiconductor nanocrystal occurs.”

However, new claim 45 does not include the recitation “determining if a fluorescence emission from the first semiconductor nanocrystal occurs.” The limitation was present in original claim 23 (now cancelled) and is present in new claim 67.

Also, as noted above and reiterated here for Applicant’s convenience, claim 67 requires applying a light source that **<u>can</u>** excite the semiconductor nanocrystal. The use of the word “can” does not necessarily require an active method step specifically requiring the light source to excite, and thereby induce emission from, the semiconductor nanocrystal; rather, the phrase “can be" merely requires the light source is capable of exciting, and thereby inducing emission from, the semiconductor nanocrystal.

C. Applicant argues on pages 12-13 of the Remarks that Mirkin et al do not use semiconductor nanoparticles.

However, Mirkin et al explicitly states that the nanoparticles “useful in the practice of the invention” include semiconductor materials (page 19, lines 24-35). Thus, Mirkin et al clearly teaches the use of semiconductor nanoparticles.

D. Applicant further argues on pages 12-13 of the Remarks that Figure 13B, which is cited in the rejections above, expressly states that the first layer are gold nanoparticles, and that gold is not a semiconductor.

However, the description of Figure 13B on page 17 of Mirkin et al merely states that the method uses “nanoparticles” and does not further state that type of material used is limited to gold.

In addition, the description of Figure 13B on page 36 states that method illustrated is “[a]n example” and uses “nanoparticles” and does not further state that type of material used is limited to gold.

Further, Example 6, which specifically uses gold nanoparticles, states that the DNA modified nanoparticles were absorbed “as shown in Figure 13B,” but does not state that Figure 13B is strictly limited to the use of gold nanoparticles.

Thus, none the three descriptions of Figure 13B strictly limit the nanoparticles depicted therein to be gold nanoparticles. Figure 13B is therefore broadly interpreted as depicting the use of any of the nanoparticles taught by Mirkin et al, including the semiconductor materials listed in page 19 (lines 24-35).

E. Applicant further agues that Mirkin et al states that gold nanoparticles are preferred for detecting nucleic acids.

However, it is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab,*

LLC, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Thus, the teaching of Mirkin et al that gold nanoparticles are **preferred** encompasses the alternate embodiment wherein the nucleic acids are detected with nanoparticles other than gold, including the semiconductor nanoparticles explicitly described by Mirkin et al as "useful in the practice of the invention" (page 19, lines 24-35). See MPEP § 2123 [R-5].

F. Applicant also argues on page 13 of the Remarks that Mirkin et al does not appear to ever use a semiconductor nanoparticle, and the rejection is therefore improper because it is based on a misinterpretation of the reference.

However, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are "useful in the practice of the invention" (page 19, lines 24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20). Thus, Mirkin et al clearly teach oligonucleotides on semiconductor nanoparticles, and the rejection is therefore proper because it is properly based on the teachings of the reference.

In addition, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

G. Applicant argues on page 13 of the Remarks that modification of Mirkin et al would move away from the preferred nanoparticle of Mirkin et al because Mirkin et al teaches detection of gold nanoparticles with the naked eye.

However, as noted above, the teaching of Mirkin et al that gold nanoparticles are **preferred** encompasses the alternate embodiment wherein the nucleic acids are detected with nanoparticles other than gold, including the semiconductor nanoparticles explicitly described by Mirkin et al as "useful in the practice of the invention" (page 19, lines 24-35).

In addition, Mirkin et al also explicitly teach that the changes are also observed spectroscopically (page 27, lines 10-15). Thus, Mirkin et al clearly also contemplates embodiments wherein detection is not performed with the naked eye.

H. Applicant further argues on pages 13-14 of the Remark that there is no motivation to modify Mirkin et al, that there is no reasonable expectation of success, and that the rejection is consequently based on improper hindsight.

However, as detailed in the rejection presented above, Weiss et al clearly teach the particles have the added benefit of allowing detection of a plurality of detectable substances without overlap of the signals (column 6, lines 35-47). Thus, Weiss et al

teach the known technique of using different semiconductor nanocrystals in each probe. In addition, Examples 1 and 2 of Weiss et al clearly teach the attachment of semiconductor nanocrystals to biological molecules (e.g., avidin in Example 1), thus providing a reasonable expectation of success for use with other biological molecules, including the nucleic acids contemplated by Weiss et al in column 6, lines 50-67.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of different probes having semiconductor nanocrystals as taught by Mirkin et al so that each probe has a different semiconductor nanocrystal as taught by Weiss et al to arrive at the instantly claimed method with a reasonable expectation of success. The modification would result in a method wherein each probe has a different semiconductor nanocrystal, wherein the nanocrystals are excited and fluoresce, and have CdS shells. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing simultaneous detection of a plurality of detectable substances without overlap as explicitly taught by Weiss et al (column 6, lines 35-47). In addition, it would have been obvious to the ordinary artisan that the known technique of using the different nanocrystals as taught by Weiss et al could have been applied to the method of Mirkin et al in with predictable results because the known technique of using the different nanocrystals as taught by Weiss et al predictably result in detection of binding events during a microarray hybridization assay.

In addition, it is also noted that under the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a **specific**

teaching, suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith* (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007).

Thus, in response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

I. Applicant further argues on page 14 of the Remarks that the equivalency of the nanoparticles of Mirkin et al and the nanoparticles of Weiss et al must be based on the prior art and not on Applicant's disclosure .

However, as noted above, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are “useful in the practice of the invention” (page 19, lines 24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20).

Further, Mirkin et al explicitly teaches a number of specific (but non-limiting) semiconductor nanoparticles (page 19, lines 24-35) that are identical to the nanocrystals disclosed by Weiss et al; e.g., ZnS, ZnTe, CdTe, InAs, and GaAs (column

5, lines 60-67 of Weiss et al). Thus, both pieces of prior art disclose the **same** nanocrystals, and are therefore equivalent.

J. Applicant continues to argue on page 14 of the Remarks that there is no evidence that gold and semiconductors are equivalent due to the preference of Mirkin et al for gold nanoparticles.

However, as noted above, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are “useful in the practice of the invention” (page 19, lines 24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20).

Further, Mirkin et al also explicitly teach that the changes in color are also observed spectroscopically (page 27, lines 10-15).

Thus, Mirkin et al clearly also contemplates embodiments wherein detection is not performed with the naked eye and semiconductor nanoparticles are used.

In addition, as also stated above, in response to applicant's arguments against the reference of Mirkin et al individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

K. Applicant argues on page 15 of the Remarks that the advantages of gold nanoparticles would be lost with semiconductor nanoparticles, and that no case for obviousness has been shown.

However, as noted above, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are “useful in the practice of the invention” (page 19, lines

24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20).

Further, Mirkin et al also explicitly teach that the changes in color are also observed spectroscopically (page 27, lines 10-15).

Thus, Mirkin et al clearly also contemplates embodiments wherein detection is not performed with the naked eye and semiconductor nanoparticles are used.

In addition, for the reasons stated above, the prior art of Mirkin et al **by itself** actually contemplates the use of semiconductor nanoparticles and spectroscopic detection of oligonucleotide nanoparticle complexes. Because the prior art of Mirkin et al **by itself** contemplates the use of semiconductor nanoparticles and spectroscopic detection of oligonucleotide nanoparticle complexes, no motivation is necessary.

In addition, it is further reiterated that in response to applicant's arguments against the reference of Mirkin et al individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

L. Applicant argues on page 15 of the Remarks that the examiner has mischaracterized the prior art of Pinkel et al because the rejection is based solely on the teachings of the Abstract, which does not explicitly refer to nucleic acids.

However, the Abstract of Pinkel et al explicitly states that the sensor has binding partners that specifically bind to **other molecules** to form a binding complex such as

nucleic acid-nucleic acid. Thus, one binding partner is one nucleic acid, and the other molecule is the other binding partner.

In addition, it is noted that Pinkel et al is not relied upon for the teaching of nucleic acids; rather Pinkel et al is relied upon for the teaching of the known technique of separately determining each binding event on an array.

In addition, as noted in the rejection above and reiterated for Applicant's convenience, claim 45 requires that each different first probe **can be** separately determined by determining if each different semiconductor nanocrystal is associated with the substrate. The use of the phrase "can be" does not necessarily require an active method step requiring the separate determination of each different semiconductor nanocrystal; rather, the phrase "can be" merely requires that each different semiconductor nanocrystal is capable of being separately detected. Because Weiss et al teach the different semiconductor nanoparticles allow detection without overlap of the signals (column 6, lines 35-47), modification of the method of Mirkin et al with the teachings of Weiss et al results in each different probe having a corresponding different semiconductor nanocrystal that is capable of being separately detected.

Thus, while not actually required by claim 45, the separate determination of whether or not each different semiconductor nanocrystal is associated with the substrate would also be obvious in view of Pinkel et al, who teach a method of assaying samples for probes by using a biosensor array to detect nucleic acid binding complexes (Abstract), wherein each binding event is separately determined; namely, simultaneous assaying of binding components of a test sample are done on by discrete detection at

individual locations (i.e., bundles of fibers; Abstract) with the added benefit that the discrete addressing assists in rapid sample identification (Abstract). Thus, Pinkel et al teach the known technique of separately determining each binding event on an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the detection of multiple different binding events as taught by Mirkin et al in view of Weiss et al so that the multiple different binding events are separately determined as taught by Pinkel et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in method having the added advantage of allowing rapid sample identification as explicitly taught by Pinkel et al (Abstract). In addition, it would have been obvious to the ordinary artisan that the known technique of using the separate determination of each binding event on an array of Pinkel et al could have been applied to the method of Mirkin et al in view of Weiss et al with predictable results because the separate determination of Pinkel et al predictably results in detection of all of the binding events during a microarray hybridization assay.

M. Applicant argues on page 16 of the Remarks that Pinkel et al is too different from Mirkin et al to provide a reasonable expectation of success and that Mirkin et al would not be characterized as a biosensor.

In response to applicant's argument that Pinkel et al is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant’s endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant

was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Pinkel et al teach the detection of nucleic acid complexes, which is also taught by Mirkin et al.

Further, Mirkin et al explicitly states that the invention is a biochip and a chemical sensor (page 57). Thus, the prior art of Pinkel et al is clearly analogous to that of Mirkin et al.

In addition, Pinkel et al clearly teach the attachment and detection of different binding partners to different groups of optical fibers (Abstract), which are a substrate. Thus, Pinkel et al clearly teach the detection of a plurality of different binding partners on a substrate, and therefore provide a reasonable expectation of success in detecting of a plurality of different binding partners on a substrate.

N. Applicant argues on pages 16-17 of the Remarks that Weiss et al does not overcome the alleged deficiencies of Mirkin et al and Pinkel et al. Because the arguments regarding Mirkin et al and Pinkel et al were not persuasive, the rejections of the claims are maintained.

O. Applicant again argues on page 16 of the Remarks that the semiconductor nanoparticles (e.g., of Weiss et al) are not equivalent to the preferred gold nanoparticles of Mirkin et al.

However, as noted above, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are “useful in the practice of the invention” (page 19, lines 24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor

nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20).

Further, Mirkin et al also explicitly teach that the changes in color are also observed spectroscopically (page 27, lines 10-15).

Thus, Mirkin et al clearly also contemplates embodiments wherein detection is not performed with the naked eye and semiconductor nanoparticles are used. Thus, modification of the teachings of Mirkin et al in view of Pinkel et al with the teachings of Weiss et al is entirely appropriate.

P. Applicant summarizes the arguments presented above on pages 17-18 of the Remarks. These arguments are addressed above.

Q. Applicant further argues on pages 18-19 of the Remarks that modification of Mirkin et al changes its mode of operation because semiconductor nanoparticles require fluorescence detection rather than detection by the naked eye.

However, as noted above, in addition to the explicit statement by Mirkin et al that semiconductor nanoparticles are “useful in the practice of the invention” (page 19, lines 24-35), Mirkin et al also explicitly teach attachment of oligonucleotides to semiconductor nanoparticles using alkanethiols (page 21, lines 20-25), as well as semiconductor nanoparticles having oligonucleotides attached thereto (page 45, lines 15-20).

Further, Mirkin et al also explicitly teach that the changes in color are also observed spectroscopically (page 27, lines 10-15).

Thus, Mirkin et al clearly also contemplates embodiments wherein detection is not performed with the naked eye and semiconductor nanoparticles are used.

In addition, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)). Thus, Applicant's argument that fluorescence can only be detected by using a suitable system (and not by the naked eye) is moot in the absence of evidence in the form of an appropriate affidavit or declaration as to the inoperability of the teachings of Mirkin et al.

R. Applicants remaining arguments regarding the dependent claims rely on the alleged deficiencies of the rejection of claim 45. These arguments are addressed above. Because the arguments regarding claim 45 were not persuasive, the rejections of the remaining dependent claims are maintained.

6. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Pearson et al (U.S. Patent No. 5,916,779, issued 29 June 1999).

Regarding claim 50, the method of claim 45 is discussed above in Section 5.

It is noted that while claim 50 requires conditions in which the enzyme **can** reverse transcribe RNA to DNA, the use of the word "can" in the claim does not necessarily require the actual reverse transcription of RNA to DNA.

While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al, Weiss et al, and Pinkel et al are silent with respect to reverse transcriptase.

However, Pearson et al teach a method of amplifying polynucleotides by contacting the sample with reverse transcriptase under conditions that reverse transcribe RNA to DNA (Abstract) with the added benefit that amplification of RNA targets is useful for monitoring upregulation of cancer genes (column 2, lines 13-25). Thus, Pearson et al teach the known technique of using reverse transcriptase, which reverse transcribes RNA to DNA.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by Mirkin et al in view of Weiss et al and Pinkel et al so that the amplification reaction is a reverse transcription of RNA to DNA using reverse transcriptase as taught by Pearson et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in amplification of RNA targets useful for monitoring upregulation of cancer genes as explicitly taught by Pearson et al (column 2, lines 13-25). In addition, it would have been obvious to the ordinary artisan that the known technique of reverse transcription of RNA to DNA using reverse transcriptase as taught by Pearson et al of could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of reverse transcription of RNA to DNA using reverse

transcriptase as taught by Pearson et al predictably results in the production of a more stable DNA target molecule from the less stable RNA molecule.

7. Claims 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999).

Regarding claims 51-53, the method of claim 45 is discussed above in Section 5.

While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to primers.

However, Fischer teaches a method for assaying a sample for a probe in the form of assaying for gene expression (Abstract) comprising incorporating the first tag sequence into the first probe polynucleotide by employing a first primer polynucleotide; namely, the sequence being detected is amplified (i.e., claim 51; Figure 1). Fischer also teaches claim 52, wherein the primer binds the polyadenlyated tail of mRNA (e.g., Figure 1, step 1; Figure 2, step 2; and column 4, lines 64-67), as well as claim 53, wherein the primer binds to a plurality of different sequences because degenerate random primers are used; column 3, lines 25-39).

The support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is

identical to a product instantly claimed is discussed above. Because Fischer teaches producing the first probe polynucleotide through amplification employing a first primer (Figure 1), and because the first probe polynucleotide must contain the tag sequence as required by claim 45, the first primer must incorporate the tag sequence into to first probe polynucleotide (otherwise, the first primer would not direct the synthesis of the first probe polynucleotide).

Fischer also teaches the added benefit that the primer allows selective amplification of members of a gene family (column 2, lines 55-60).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by Mirkin et al in view of Weiss et al and Pinkel et al so that the amplification comprises the primers as taught by Fischer to arrive at the instantly claimed method with a reasonable expectation of success. The modification would result in using primers having the tags therein (i.e., claim 51), a polyadenlyated tail of mRNA (i.e., claim 52), and primers that bind to a plurality of different sequences (i.e., claim 53). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing selective amplification of members of a gene family as explicitly taught by Fischer (column 2, lines 55-60). In addition, it would have been obvious to the ordinary artisan that the known technique of using the primers as taught by Fischer of could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of

using the primers as taught by Fischer predictably results in the reliable amplification of the probe polynucleotide.

8. Claim 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 53 above, and further in view of Caetano-Anolles (U.S. Patent No. 5,962,221, issued 5 October 1999).

Regarding claim 54, the method of claim 53 is discussed above in Section 7.

While Fischer teaches degenerate primers (column 3, lines 25-39), neither Mirkin et al, Pinkel et al, Weiss et al, nor Fischer teach the four 3' residues are degenerate.

However, Caetano-Anolles teaches primers (i.e., SSR primers) having degenerate 3' ends of 4 residues (e.g., 2 to 10 nucleotides in length) with the added advantage of allowing detection of polymorphisms (column 3, lines 22-31). The instantly claimed 4 bases is an obvious variant the 2-10 nucleotides as taught by Caetano-Anolles. Thus, Caetano-Anolles teaches the known technique of using primers having degenerate 3' ends of 4 residues.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with degenerate primers as taught by Mirkin et al, Pinkel et al, Weiss et al and Fischer by using the 3' degenerate primers as taught by Caetano-Anolles to arrive at the

instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of polymorphisms as explicitly taught by Caetano-Anolles (column 3, lines 22-31). In addition, it would have been obvious to the ordinary artisan that the known technique of using the 3' degenerate primers as taught by Caetano-Anolles could have been applied to the method of Mirkin et al in view of Weiss et al, Pinkel et al, and Fischer with predictable results because the known technique of using the 3' degenerate primers as taught by Caetano-Anolles predictably results in the reliable amplification of the probe polynucleotide.

9. Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999), Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 53 above, and further in view Kambara et al (U.S. Patent No. 5,985,556, issued 16 November 1999).

Regarding claim 55, the method of claim 53 is discussed above in Section 7.

It is noted that while claim 55 requires bases that **can** base pair with more than one different base, the use of the word "can" in the claim does not necessarily require base pairing with a different base.

While Fischer teaches primers comprising bases that bind more than one base (e.g., inosine, column 3, lines 25-39), neither Mirkin et al, Pinkel et al, Weiss et al, nor Fischer teaches bases at the four 3' residues are degenerate.

However, Kambara et al teach a method of detecting a first probe in a first sample (e.g., sequencing a DNA fragment; Abstract) comprising a primer having inosine at the fourth position of the 3' end of a primer with the added advantage of enhancing selectivity (column 31, lines 15-30). The instantly claimed "bases at the four 3' residues," which is broadly interpreted as being more than one base of the four 3' bases, is therefore an obvious variant of the one inosine at the fourth position as taught by Kambara et al.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with degenerate primers as taught by Mirkin et al, Pinkel et al, Weiss et al, and Fischer so that the degenerate primer comprises more than one base that can base pair with more than one different base in the four 3' residues as taught by Kambara et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a primer having inosine at the fourth position of the 3' end of a primer with the added advantage of enhancing selectivity as explicitly taught by Kambara et al (column 31, lines 15-30). In addition, it would have been obvious to the ordinary artisan that the known technique of using the degenerate primer comprising more than one degenerate base as taught by Kambara et al could have been applied to

the method of Mirkin et al in view of Weiss et al, Pinkel et al, and Fischer with predictable results because the known technique of using the degenerate primer comprising more than one degenerate base as taught by Kambara et al predictably results in the reliable amplification of the probe polynucleotide.

10. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Hunkapiller et al (U.S. Patent No. 5,942,609, issued 24 August 1999).

Regarding claim 56, the method of claim 45 is discussed above in Section 5.

Mirkin et al, Pinkel et al, and Weiss et al do not teach ligation.

However, Hunkapiller et al teach a method of detection of polynucleotides on solid supports (Title) comprising the ligation of polynucleotide sequences into oligonucleotides (column 3, line 50-column 4, line 33) with the added advantage that ligation (i.e., using DNA ligase) provides a proof-reading advantage that produces the correct ligation product (column 5, lines 21-25). thus, Hunkapiller et al teach the known technique of ligation.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Weiss et al and Pinkel et al so that the tag sequence is incorporated into the

probe using as taught by Hunkapiller et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a proof-reading advantage that produces the correct ligation product as explicitly taught by Hunkapiller et al (column 5, lines 21-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using ligation to generate a probe polynucleotide as taught by Hunkapiller et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of using ligation to generate a probe polynucleotide as taught by Hunkapiller et al predictably results in the reliable synthesis of the probe polynucleotide.

11. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Agrawal et al (U.S. Patent No. 5,652,103, issued 29 July 1997).

Regarding claim 57, the method of claim 45 is discussed above in Section 5.

Mirkin et al, Pinkel et al, and Weiss et al do not teach terminal transferase.

However, Agrawal et al teach a method of detecting a first probe in a first sample (e.g., determining nucleotide sequences; Abstract) wherein polynucleotides sequences are incorporated into oligonucleotides using terminal transferase with the added benefit that terminal transferase provides an efficient and reliable method for producing a

molecule of suitable length for sequencing (column 3, lines 8-15). Thus, Agrawal et al teach the known technique of using terminal transferase

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Weiss et al and Pinkel et al so that the tag sequence is incorporated into the probe using terminal transferase as taught by Agrawal et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in providing an efficient and reliable method for producing a molecule of suitable length for sequencing as explicitly taught by Agrawal et al (column 3, lines 8-15). In addition, it would have been obvious to the ordinary artisan that the known technique of incorporating the tag into the probe using terminal transferase as taught by Agrawal et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of incorporating the tag into the probe using terminal transferase as taught by Agrawal et al predictably results in the reliable synthesis of the probe polynucleotide.

12. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Cleuziat et al (U.S. Patent No. 5,849,547, issued 15 December 1998).

Regarding claim 60, the method of claim 45 is discussed above in Section 5.

While Mirkin et al also teach the first probe comprises a base which is not selected from the group consisting of adenine, guanine, cytosine, thymine, and uracil (e.g., the linking oligonucleotide contains modified bases; page 23, lines 14-24), neither Mirkin et al, Pinkel et al, nor Weiss et al specifically teach the tag sequence comprises a base other than A,G,T,C, and U (i.e., hybridization of a probe to the modified base).

However, Cleuziat et al teach a method of detecting nucleic acids (e.g., amplifying target nucleic acids; Abstract) comprising hybridization to sequences containing modified bases with the added advantage that the resulting duplex exhibits greater stability (column 23, lines 29-34). Thus, Cleuziat et al teach the known technique of using bases other than A,G,T,C, and U.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising hybridization of the first tag sequence as taught by Mirkin et al in view of Pinkel et al and Weiss et al so that the tag sequence comprises bases with bases other than A, G, C, T, and U as taught by Cleuziat et al to arrive at the instantly claimed method with a reasonable

expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in the resulting duplex exhibiting greater stability as explicitly taught by Cleuziat et al (column 23, lines 29-34). In addition, it would have been obvious to the ordinary artisan that the known technique of using bases other than A,G,T,C, and U as taught by Cleuziat et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of using bases other than A,G,T,C, and U as taught by Cleuziat et al predictably results in the reliable probes for hybridization.

13. Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Klinger et al (U.S. Patent No. 5,693,783, issued 2 December 1997).

Regarding claim 64, the method of claim 45 is discussed above in Section 5.

While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al, Pinkel et al ,and Weiss et al are silent with respect to metaphase chromosomes.

However, Klinger et al teach hybridization of probes to metaphase spreads of chromosomes (column 4, lines 23-27) with the added benefit of diagnosing

chromosomal aneuploidies (column 2, lines 60-63). Thus, Klinger et al teach the known technique of hybridizing to target metaphase chromosomes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al to that the targets are the metaphase chromosome spread as taught by Klinger et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in diagnosing chromosomal aneuploidies as explicitly taught by Klinger et al (column 2, lines 60-63). In addition, it would have been obvious to the ordinary artisan that the known technique of hybridizing to target metaphase chromosomes as taught by Klinger et al could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of hybridizing to target metaphase chromosomes as taught by Klinger et al predictably results in the use of targets useful in detecting genetic diseases.

14. Claims 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) as applied to claim 45 above, and further in view of Lebo (U.S. Patent No. 5,665,540, issued 9 September 1997).

Regarding claim 65, the method of claim 45 is discussed above in Section 5.

While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to interphase nuclei.

However, Lebo teaches the hybridization of probes to interphase nuclei with the added advantage of allowing the counting of adjacent gene copies and detection gene deletion (column 4, lines 38-50). Thus, Lebo teaches the known technique of using targets in interphase nuclei.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al so that the target is in the interphase nuclei as taught by Lebo to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing the counting of adjacent gene copies and detection gene deletion as explicitly taught by Lebo (column 4, lines 38-50). In addition, it would have been obvious to the ordinary artisan that the known technique of hybridizing to targets in interphase nuclei as taught by Lebo could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of hybridizing to targets in interphase nuclei as taught by Lebo predictably results in the use of targets useful in detecting genetic diseases.

Regarding claim 66, the method of claim 45 is discussed above in Section 5.

While Mirkin et al also teach the method wherein the target is a polynucleotide is located in a tissue (page 24, lines 18-20), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to fixed tissues.

However, Lebo teaches the hybridization of probes to cells that have been fixed (e.g., column 16, Example I) with the added advantage that fixing cells to slides minimizes false negative results (column 3, lines 17- 22). Thus, Lebo teaches the known technique of using targets in fixed tissues.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of detection in cells as taught by Mirkin et al in view of Pinkel et al and Weiss et al so that the cells are fixed cells to arrive at the instantly claimed method as taught by Lebo with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in minimization of false negative results as explicitly taught by Lebo (column 3, lines 17-22). In addition, it would have been obvious to the ordinary artisan that the known technique of hybridizing to targets fixed cells as taught by Lebo could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of hybridizing to targets in fixed cells as taught by Lebo predictably results in the minimization of false negative results.

15. Claim 73 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997)) as applied to claim 45 above, and further in view of Kohne (U.S. Patent No. 5,612,183, issued 18 March 1997).

Regarding claim 73, the method of claim 45 is discussed above in Section 5.

Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to determining the amount of the probe present in the sample.

However, Kohne teaches a method of hybridizing nucleic acids that determines the amount of probe in a sample (i.e., a method of determining the degree of and quantitating nucleic acid hybridization, Abstract) with the added advantage that the quantitation allows detection of the sensitivity of organisms to antimicrobial agents (column 12, lines 17-33). Thus, Kohne teaches the known technique of determining the amount of the probe present in the sample.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising detection as taught by Mirkin et al in view of Pinkel et al and Weiss et al so that detection comprises determining the amount of probe present as taught by Kohne to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of the sensitivity of organisms to antimicrobial agents as explicitly taught by Kohne (column 12, lines 17-33). In addition, it would have been

obvious to the ordinary artisan that the known technique of determining the amount of the probe present in the sample as taught by Kohne could have been applied to the method of Mirkin et al in view of Weiss et al and Pinkel et al with predictable results because the known technique of determining the amount of the probe present in the sample as taught by Kohne predictably results in the quantitation of the assay results.

Response to Arguments

Applicants remaining arguments regarding the dependent claims rely on the alleged deficiencies of the rejection of claim 45. These alleged deficiencies are addressed in Section 5 above. Because the arguments regarding claim 45 were not persuasive, the rejections of the remaining dependent claims are maintained.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Robert T. Crow/
Examiner, Art Unit 1634

Robert T. Crow
Examiner
Art Unit 1634